

Scientific consensus – “Addiction”

- Influence of nicotine and other tobacco smoke constituents on smoking behavior as a determinant of smoke exposure -

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I. Objectives of the project

The objectives of the project are to clarify

- 1) current scientific understanding of addiction among PM scientists,
- 2) how nicotine and/or smoking fit into this understanding,
- 3) the extent to which nicotine determines smoke exposure, and
- 4) thereby to contribute to potential product modifications by the 3rd quarter of 2000.

The participants and their scientific background by training are as follows (in an alphabetical order of the family name):

Carchman, Richard: pharmacology
Davies, Bruce: molecular pharmacology/biochemistry
Gullotta, Frank: experimental/physiological psychology
Ritter, Mitchel: clinical psychology
Takada, Kohji: behavioral pharmacology.

The "team" was formed in February 2000, and this manuscript represents our current understanding and future plans on this issue by the team as of August 2000.

II. Current understanding of the concept of "addiction"

Our initial efforts at generating a single scientific definition of addiction proved extremely difficult, as what was suggested reflected perspectives from the different disciplines of the participants. Not surprisingly, this also reflected the diversity of the literature on addiction¹. This mutual educational process resulted in the realization that a pluri-disciplinary approach offered a far richer path towards understanding what is essentially a multidimensional question.

The PM website states that "Cigarette smoking is addictive, as that term is most commonly used today."² We concur with this position³. However, the statement does not provide

¹ For definitions by public health authorities see Appendix A. As for changes in definition as seen in the representative pharmacological textbook see Appendix B.

²URL: <http://www.philipmorris.com>

As for various definitions in various languages and historic changes of the definition of the term as nonscientific usage, see Appendix C. As for the evolution/history of PM position on the term addiction and the "position" of nicotine and/or smoking, see Appendix D.

³Current usage of the term by non-scientists appears to connote the following:

A repetitive behavior suggesting a "loss of control", which may have a positive (e.g. "health food" addict) or a negative ("junk food" addict) outcome.

insight into the key question of the relationships between smoking behavior, exposure, and harm reduction.

We achieved consensus in a number of areas that we believe would be informative and thereby enable us to develop and implement harm reduction strategies. As part of this consensus, we adopted, as an operating principle, to approach these factors individually, but to understand them collectively. These include:

- Smoking involves very complex psychological and social behaviors.
- Nicotine is a centrally as well as a peripherally active compound.
- The pharmacological effects of nicotine are important, but are probably not the sole determinant of smoking behavior.
- Recent scientific findings suggest other tobacco smoke chemicals by themselves or by potentially modulating the effects of nicotine, may possess central and/or peripheral effects relevant to smoking behavior and exposure.

Examples - Areas to cover:

- CNS pharmacology – stimulation of nicotinic acetylcholine receptors
- Peripheral pharmacology – cardiovascular effects
- Sensory aspects – stimulation of afferent nerves
- Psychological aspects – affect management
- Sociological aspects – facilitation of social interactions
- Developmental aspects – continuum from initiation to cessation

III. Addiction or smoking behavior as a determinant of exposure? – our working model

Regarding “addiction” or “addictive behaviors”, the following descriptions in the field of clinical psychology⁴ would be relevant to depict the broad spectrum of the issue:

- “Drug abuse and addiction have been considered the consequence of a complicated blend of biological, psychological and sociological factors. In short, drug abuse and addiction reside neither in the drug nor in the personality of the user.”
- “Addictive behaviors are the result of any interactive factors that vary in prominence from individual to individual. It is essential to take a multidimensional view of drug use, abuse and addiction; the psychological determinants of drug use, the developmental

Public Health Authorities appears to use the term to connote:

A repetitive behavior associated with an adverse health outcome, suggesting a “loss of control” attributable to some inherent characteristic or property of the substance and/or behavior.

⁴ Shaffer HJ and Jones SB, “Quitting Cocaine: The Struggle Against Impulse”, Lexington Books, pp. 37-77, 1989

phase in which abuse occurs, the social and cultural contexts in which toxicants are used and abused, and the pharmacological properties of the substance."

In order to capture the spectrum that is involved in smoking behavior *per se*, the following description in the field of psychiatry/psychopharmacology⁵ would be relevant:

"Despite decades of research into motives for tobacco smoking, the question of why people smoke is still a challenge. The critical role of nicotine dependence has recently been acknowledged [*reference omitted*]. However, it is also clear that the interactions among the psychosocial, sensory, and pharmacologic reinforcing mechanisms are complex [*reference omitted*] and their relative roles unknown."

Our operating principles for approaching smoking behavior⁶ as the determinant of exposure is as follows:

- As the above quotations summarize, our consensus defines/considers addiction as a complex, highly interactive behavior which must be considered in light of those interactions rather than from a purely reductionist perspective. When considering smoking, it is for this reason that smoking behavior becomes the more appropriate term rather than the term addiction. With respect to exposure and in view of our position that smoking behavior is the determinant of exposure, a careful study applying our operating principles appears to be the most promising approach towards developing, and contributing to the harm reduction program.
- Therefore, a successful approach is based on the analysis of individual components of smoking behavior coupled with a collective understanding. In addition to the "examples - areas to cover" described above, necessary data may also be obtainable from the following topics:
 - Cessation program, e.g. pharmacotherapy, behavior modification
 - Multi-substance use: patterns of behavior, substitution (physical dependence)
 - Substance-prone personality
 - Factors determining "chippers"
 - Other substance-related behavior, e.g. role of the alleviation of withdrawal signs.

IV. Smoking behavior as the overall determinant to exposure

Smoke exposure (ETS aside) is determined by some of the following behaviors, e.g. the choice to smoke or not to smoke, selection of the brand, and smoking topography. We

⁵ Fagerstrom KO, Schneider, NG, Measuring nicotine dependence: a review of the Fagerstrom tolerance questionnaire, J Behav Med 12: 159-182 (1989)

⁶ for definition of smoking behavior see Chap IV.

have not discussed smoking topography since this is being addressed by the "consensus - compensation" group.

Individual components of smoking behavior (including smoking topography) can be covered by the following areas:

- Pharmacology
- Psychology
- Sociology
- Developmental aspects

These comprise the individual components that define smoking behavior operationally. Our understanding of smoking behavior, as it relates to exposure, requires their integration if we are going to succeed in achieving significant harm reduction. Possible outcomes of the examination through these components are as follows:

Pharmacological components

Current scientific thinking suggests that nicotine plays a significant role in smoking behavior, and therefore exposure to smoke constituents. It is not known whether other active components of tobacco smoke exist in a form which would also influence smoking behavior. It is therefore of considerable importance, in terms of harm reduction, to characterize as precisely and completely as possible, the effect of nicotine on smoking behavior, to identify other potential smoke constituents, and to understand their differential effects. Once we have a more complete understanding of the factors involved, the following can be considered:

- Possible reformulation of our products that might modify the pharmacological effect of smoke constituents on smoking behavior.
- Develop theoretical and ultimately experimental models, reflecting the complex interactions between active constituents in tobacco smoke and factors operative in smoking behavior (see above), further contributing to reducing smoke exposure.

Psychological components

Many researchers involved in the fields of psychology regarding substance use and abuse suggest that the origins of this behavior lie in the psychological dynamics⁷ of the user. This may involve aspects of affect management, coping strategies, stress reduction, cognitive enhancement and so forth.

Understanding the conditions under which our products are consumed should provide us with a better understanding of how exposure is determined by the consumer themselves, first independently of the pharmacological properties of our products, their effects and potential, and then in conjunction, in light of our interactive model.

In short, by elucidating the psychological factors involved in the use of our product may

⁷ Pharmacological effects may contribute to this dynamics.

provide insights into its consumption, thereby contributing to a long-term harm reduction.

Sociological components

Smoking behavior, particularly as it relates to initiation – though not excluding other moments in the smoking career - is greatly influenced by the human context surrounding it. Factors such as family, peer group, socio-economic level, social activities all may play significant roles in the development of smoking behavior, and therefore the exposure.

Though difficult to reduce to specific mechanisms, understanding the interactions between our product, its perception and use in society as a whole, as well as in specific sub-groups, will enhance our ability to perceive the phenomenon in all its complexity. Further, it may allow us to propose and execute means towards better prevention of smoking by minors and enabling smokers to make decisions about a risky product destined for use by an adult population.

Developmental aspects

Current scientific thinking suggests that specific periods of life constitute moments when the potential for substance use is higher than others. Smoking can be seen as developmental process where the subject passes through different phases, from experimentation, initiation into "confirmation" and maintenance and possibly culminating in cessation, under the influence of various other factors including those in other components described above. For example dose or exposure level may play a critical role in this process, however, determining factors for each transition as they relate to the specific periods of life have yet to be elucidated. A better understanding of these factors may enable us to reduce their effects during critical periods.

V. What do we know about smoking behavior?

This section summarizes what is known about each component of smoking behavior as defined above. This will also provide current knowledge on one of the objectives of this project, i.e. to clarify the extent to which nicotine determines smoke exposure, which can be rephrased into "to what extent nicotine controls such smoking behaviors."

Role of nicotine as it relates to the control of smoke exposure⁸

Pharmacodynamics

Reinforcing effects of nicotine

Positively reinforcing effects of intravenous nicotine have been reported in various species of animals and in humans but the general consensus appears to be that the reinforcing efficacy of nicotine is weak. Aversive effects of intravenous nicotine have also been reported in monkeys and in humans at the same dose level as the positively reinforcing doses. These make the interpretation on the role of nicotine in controlling

⁸ For more detailed review of the literature, see Appendix E.

smoking behavior difficult, and appear to support our notion that though important, nicotine probably is not the sole determinant of smoke exposure, at least for a population at large.

Biochemical changes in the brain induced by nicotine

As for the mechanism underlying drug reward, the stimulation of mesolimbic dopaminergic system has been considered to play a crucial role. In rodents, nicotine has been reported to increase the extracellular level of dopamine in this brain region that is often interpreted as the evidence for the "addictiveness" of nicotine. However, whether or not the similar change in midbrain dopaminergic system will be observed in nonhuman primates is not clear, not to mention humans. For example, raclopride, a D2 antagonist, has been reported to do very little in the monkey brain⁹. Thus it can be said that not much is known on the brain mechanism(s) underlying the reinforcing effects of nicotine.

Withdrawal signs after chronic nicotine treatment and smoking cessation

Although some withdrawal signs have been reported after chronic treatment of nicotine in rodents, it appears to be a general agreement among researchers that the detection of nicotine withdrawal signs in rodents is difficult. Further, no apparent sign has been observed in monkeys. These data appear to indicate that the physical dependence potential of nicotine is weak in nature. In humans, various signs have been reported to be observed upon cessation of smoking and disease criteria have been established both in ICD-10 by WHO¹⁰ and DSM-IV by APA¹¹ (see Appendix F). However, it has been reported that de-nicotinized cigarettes also alleviated withdrawal signs in humans. Thus it appears that to what extent the withdrawal signs observable upon smoking cessation are pharmacologically mediated requires further studies.

Pharmacological intervention of smoking behavior

The results of treatments of nicotine and a centrally-acting specific nicotinic antagonist mecamylamine on smoking behavior, and pharmacotherapy of smoking behavior or pharmacological aids for smoking cessation will be summarized and will be discussed in relation to the role of nicotine in smoking behavior or exposure.

Effect on cognition, memory and "mood"

Effects of nicotine on cognition, memory, and "mood" both in animals and humans will be summarized and their possible role in smoking behavior or exposure will be discussed.

⁹ Domino, personal communication (2000).

¹⁰ The World Health Organization, The ICD-10 Classification of Mental and Behavioral Disorders: Clinical Descriptions and Diagnostic Guidelines, 1992.

¹¹ American Psychiatric Association, Diagnostics and Statistical Manual of Mental Disorders DSM-IV, 1994.

Neuronal nicotinic acetylcholine receptors in the brain

Configuration of the neuronal nicotinic acetylcholine receptors (nAChR), their distribution in the brain, and their functions are being studied vigorously. However, despite the accumulation of the significant body of knowledge, much remains to be elucidated. Current status of the knowledge will be briefly summarized and discussed.

Pharmacokinetics

Absorption, fate, and excretion of nicotine will be summarized.

Peripheral effects

Effects on peripheral nervous system via ganglion cells, neuromuscular junctions, and adrenal medulla will be summarized. Role of sensory stimulation on smoking behavior will be summarized also.

Genetic predisposition

Genetic polymorphism of CYP2A6, a major metabolizing enzyme of nicotine, will be summarized and discussed in relation to smoking behavior and exposure. Genetic predisposition regarding multi-substance use and other substance-related behavior will also be discussed and summarized.

Psychological aspects

Non-pharmacologic role/function of smoking behavior on affect management, cognitive enhancement and coping will be discussed and summarized.

Sociological aspects

Effect of family composition, peer group, socio-economic level and educational level on smoking behavior will be discussed and summarized.

Developmental aspects

Developmental aspects on initiation, "confirmation", maintenance, cessation, and relapse will be discussed in conjunction with the role of the above components.

VII. What needs to be done?

In order to achieve the objectives, we propose the following:

Establish permanent smoking behavior group

Due to the rapid developments on understanding of each component of smoking behavior, e.g. function of neuronal nicotinic acetylcholine receptors, constant monitoring/analysis of the developments appears necessary in order to cope with various existing and emerging issues as well as to contribute to the improved harm-reduction strategies. Therefore the establishment of a group focusing on various

aspects of smoking behavior, e.g. with quarterly update of the developments, would be beneficial. It will also enable us to reach out to the scientific and academic communities working in the different, though related, fields. The "immediate" goals of the group, when the proposal described in this section is achieved, will include:

- Prediction on whether or not alteration of the nicotine content in the smoke results in reduction in smoke exposure.
- Further analysis on the role of nicotine in smoking behavior.
- Analysis of smoke constituents which by themselves modulate neurochemical activity (peripheral as well as central) or modulate the effects of nicotine.
- Analysis of smoking behavior in broader spectrum.

Integration of consensus addiction and consensus compensation

Since both projects cannot be mutually exclusive and will eventually give some answers on the controlling factors of smoke exposure and to a question why people smoke, the integration of these projects appears necessary for a detailed analysis with a broader view which will eventually lead us to guide reduced harm products.

Interface with Total Exposure Study

Many of the questions raised in this manuscript will potentially be answered by the Total Exposure Study planned, and we believe the information from the proposed smoking behavior group will help determine improved research plans and analysis of the results.

Gap analysis

Current team somewhat lacks detailed understanding of the individual components of smoking behavior especially psychological, sociological, and developmental aspects. These are the areas, which require a detailed gap analysis. The analysis will also give us insights into e.g. what research to support.

Multi-disciplinary workshops

It will be very helpful to have multi-disciplinary workshops on some of the issues with open questions, e.g. to find and fill the "gaps", and the results can be directly fed back to our understanding on factors controlling smoking behavior and exposure.

Support external investigation

Supporting the External Research Program as a group, by reviewing research proposals and providing comment, may also help identify the "gap" and will eventually help elucidate the necessary experimental works.

Reflection (understanding collectively)

The information obtained from the above can only be utilized by the collective understanding, which may be achievable by e.g. quarterly meetings by the proposed team.

Integration into the harm reduction program

Since the ultimate goal of this team is to contribute to the production of reduced harm products, the overall outcome based on above should be integrated into the harm reduction program.

Appendix A. Definitions by public health authorities**A-1. Reports of WHO Expert Committee on Drug Dependence****WHO Expert Committee on Addiction-producing Drugs 7th Report (1957)**

Drug addiction is a state of periodic or chronic intoxication produced by the repeated consumption of a drug (natural or synthetic). Its characteristics include:

- (1) an overpowering desire or need (compulsion) to continue taking the drug and to obtain it by any means;
- (2) a tendency to increase the dose;
- (3) a psychic (psychological) and generally a physical dependence on the effects of the drug;
- (4) detrimental effect on the individual and on society.

(WHO Technical Report Series 116, 1957)

WHO Expert Committee on Addiction-producing Drugs 13th Report (1964)

Following description is found under the title of "Drug dependence" to replace the terms "drug addiction" and "drug habituation":

- "The Expert Committee sought also to differentiate addiction from habituation and wrote a definition of the latter which, however, failed in practice to make a clear distinction. The definition of addiction gained some acceptance, but confusion in the use of the terms addiction and habituation and misuse of the former continued.Hence, the use of the term "drug dependence", with a modifying phrase linking it to a particular drug type in order to differentiate one class of drugs from another, has been given most careful consideration."
- "It must be emphasized that drug dependence is a general term selected for its applicability to all types of drug abuse and carries no connotation of the degree of risk to public health or need for a particular type of drug control."
- As for the types of drugs of dependence, the report classifies barbiturates, cocaine, amphetamine, and cannabis.
- "Dependence" is defined as "a state, psychic and sometimes also physical, resulting from the interaction between a living organism and a drug, characterized by behavioral and other responses that always include a compulsion to take the drug on a continuous or periodic basis in order to experience its psychic effects, and sometimes to avoid the discomfort of its absence. Tolerance may not be present. A person may be dependent on more than one drug." (this definition was adopted in ICD-10, 1992)
(WHO Technical Report Series No. 273, 1964; the name of the committee was thereafter changed to WHO Expert Committee on Drug Dependence)

A-2. US Surgeon General's Reports (SGR) 1964 and 1988**SGR, 1964**

"Drug addiction is a state of periodic or chronic intoxication produced by the repeated consumption of a drug (natural or synthetic). Its characteristics include:

- an overpowering desire or need (compulsion) to continue taking the drug and to obtain it by any means;
- a tendency to increase the dose;
- a psychic (psychological) and generally a physical dependence on the effects of the drug;
- detrimental effect on the individual and on society."

SGR, 1988

- "In this Chapter the term "drug dependence" or "drug addiction" refers to self-administration of a psychoactive drug in a manner that demonstrates that the drug controls or strongly influences behavior."
- "The term "drug addiction" and "drug dependence" are scientifically equivalent; both terms refer to the behavior of repetitively ingesting mood-altering substances by individuals. The term "drug dependence" has been increasingly adopted in the scientific and medical literature as a more technical term, whereas the term "drug addiction" continues to be used by NIDA and other organizations when it is important to provide information at a more general level."

Detailed comparison¹²**1. Definition**

Same in Both: Compulsive use required in both definitions

Differences between two definitions:

1964	1988
Distinction made between a habit and addiction.	No distinction between a habit and addiction
Tolerance (tendency to increase dose) required .	Tolerance may occur but <u>not</u> required
Psychic (psychological) and physical dependence (i.e., withdrawal) required .	Psychic and physical dependence may occur but <u>not</u> required (i.e., not necessary that withdrawal occurs).
Psychoactive effects implied but not specified.	Must produce psychoactive effects.
Chronic or periodic intoxication (i.e., euphoria) required .	May produce euphoria but <u>not</u> necessary.
Detrimental effects on the individual <u>and</u> society required.	Use despite harmful effects may occur but <u>not</u> required.
Criterion of drug-reinforced behavior implied but not specified.	Must have drug-reinforced behavior.
Stereotypic patterns of use not specified.	Stereotypic patterns of use may occur but <u>not</u> required.

It should be noted that the 1964 criteria were objective and quantifiable, whereas the 1988 criteria are, for the most part, subjective and not readily quantifiable.

¹² Prepared by Gullotta, 1999.

2. Definitions as applied to smoking and nicotine:

<u>1964</u>	<u>1988</u>
Smoking viewed as habit.	Smoking viewed as addiction.
Acute but not chronic tolerance demonstrated with smoking (Edmunds, 1916; West and Russell, 1987, 1988).	Smoking shown by some experimenters to produce both acute and chronic tolerance and/or sensitization (Benowitz, 1992; Perkins, 1995).
Smoking not shown to produce physical dependence (i.e., no well-defined withdrawal symptoms like noted with the opiates). (WHO, 1957)	Smoking has been claimed to produce both psychic and physical dependence (Benowitz, 1992).
Psychoactive effects in response to smoking implied by studies demonstrating EEG effects of smoking (Lambiase, 1957).	Smoking produces psychoactive effects such as EEG effects and effects on behavior (Pritchard, Robinson et al, 1991).
No intoxication had been demonstrated with smoking (WHO, 1957).	Some researchers (e.g., Pomerleau, 1992 and Henningfield (see Soria, 1996) claim intoxication (i.e., euphoria) is produced by nicotine and/or smoking.
Smoking not shown to produce harm on society (WHO, 1957).	Researchers argue that smoking produces detrimental effects on the individual <u>and</u> society (US Dept. of Health and Human Services, 1986).
Drug-reinforced behavior not a criterion for addiction in 1964 (WHO, 1957).	Drug-reinforced behavior (i.e., IVSA) in response to nicotine has been demonstrated (Risner and Goldberg, 1983).
Stereotypic patterns of behavior not defined as criterion for addiction in 1964.	Stereotypic patterns of use observed with smoking (US Dept. of Health and Human Services, 1988, pp. 7-8). (Note: Stereotypy is characteristic of well-learned habits (Kihstrom, 1987)

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A-3. UK Royal Society of Physicians London 2000

- “Addiction’ and ‘dependence’ are terms whose definition has a social as well as a scientific dimension. In principle, they may be distinguished, but in practice such a distinction serves little purpose and the terms are used interchangeably here....Under the current definition, the terms refer to a situation in which a drug or stimulus has unreasonably come to control behavior”.
- Earlier and popular view: “addiction refers to a state in which an individual needs to continue to take a drug in order to stave off unpleasant or dangerous withdrawal effects”. “..it addresses just one aspect of a wider problem”.
- Intoxication: “This feature no longer appears in any official definition because it is apparent that it is neither a necessary nor a sufficient condition...”
- Criteria for addiction given:
 1. A strong desire to take the drug;
 2. Substance taken in larger amounts or longer than intended;
 3. Difficulty in controlling use;
 4. A great deal of time is present in obtaining, using or recovering from effects of substance;
 5. A higher priority given to drug use than to other activities and obligations;
 6. Continued use despite harmful consequences;
 7. Tolerance: absence of nausea, dizziness and other characteristics;
 8. Withdrawal;
- “...therefore that no single set of criteria can provide a universal framework for the definition of dependence or addiction”.

**Appendix B. Goodman's and Gilman's The Pharmacological Basis of Therapeutics
1975-1996**

Note: bold letters by Takada.

Summary

Description in Goodman's and Gilman's The Pharmacological Basis of Therapeutics, a representative pharmacology textbook, appears to have been the mixture of the position of WHO Expert Committee on Drug Dependence and that of the US Surgeon General's Reports. For example, Dr. Jaffe described in the 8th Edition that "Addiction is used to connote a severe degree of drug dependence that is an extreme on a continuum of involvement with drug use." (1990). Dr. O'Brien, taking over the chapter in the 9th Edition, appear to have more inclination towards the "disease criteria", i.e., "The term addiction, when used in this chapter, will refer to compulsive drug use, the entire substance dependence syndrome as defined in DSM IV." (1996). Thus it appears that the definition of the term addiction fluctuates even in the representative textbook of pharmacology.

5th ed., 1975 (by Jaffe, JH) states the followings:

- "Compulsive Drug use. One of the hazards in the use of drugs to alter mood and feeling is that some individuals eventually behave as *if the effects produced by a drug, or the conditions associated with its use, are necessary to maintain an optimal state of well being*. Such individuals are said to have a *psychological dependence on the drug (habituation)*. The intensity of this dependence may vary from a mild desire to a "craving" or "compulsion" to use the drug. This need or psychological dependence may then give rise to behavior (compulsive drug use) characterized by a preoccupation with the use and procurement of the drug."
- "Compulsive drug use is usually detrimental both to the user and to the society of which he is a part."
- "*Physical dependence* refers to an altered physiological state produced by the repeated administration of a drug, which necessitates the continued administration of the drug to prevent the appearance of a stereotyped syndrome, *the withdrawal or abstinence syndrome*, characteristic for the particular drug."
- "Addiction. It is possible to describe all known patterns of drug use without employing the terms addict or addiction. In many respects this would be advantageous, for the term addiction, like term abuse, has been used in so many ways that it can no longer be employed without further qualification or elaboration. However, since it is not likely that the term will be dropped from the language, it is appropriate to make an effort to delimit its meaning. The definition used here is somewhat arbitrary, and it is not necessarily identical with other definitions of addiction or drug dependence (see Eddy et al., 1965; National Commission, 1973; World Health Organization, 1973). In this

chapter, the term addiction will be used to mean a behavioral pattern of compulsive drug use, characterized by overwhelming involvement with the use of a drug, the securing of its supply, and a high tendency to relapse after withdrawal. Addiction is thus viewed as an extreme on a continuum of involvement with drug use and refers in a quantitative rather than a qualitative sense to the degree to which drug use pervades the total life activity of the user. In most instances it will not be possible to state with precision at what point compulsive use should be considered addiction. Anyone who is addicted would be considered drug dependent within the WHO definitions, but within the set of definitions used here the term addiction cannot be used interchangeably with physical dependence. It is possible to be physically dependent on drugs without being addicted and to be addicted without being physically dependent (see below)." (bold by Takada)

7th ed., 1985 (by Jaffe, JH):

- "The term addiction will be used to mean a behavioral pattern of drug use, characterized by overwhelming involvement with the use of drug (compulsive use), the securing of its supply, and a high tendency to relapse after withdrawal. Addiction is thus viewed as an extreme on a continuum of involvement with drug use and refers in a quantitative rather than a qualitative sense to the degree to which drug use pervades the total life activity of the user **and to the range of circumstances in which drug use controls his behavior.**" (bold by Takada, showing the difference in description from 1975 edition).

8th ed., 1990 (by Jaffe, JH)

- "Drug dependence can be defined as a syndrome in which the use of a drug is given a much higher priority than other behaviors that once had higher value. The dependence syndrome is not absolute, but exists in degrees, and its intensity is gauged by the behaviors that are associated with the use of the drug. No sharp line separates drug dependence from nondependent but recurrent drug use. In its extreme form, drug dependence is associated with compulsive drug-using behavior, and it exhibits the characteristics of a chronic relapsing disorder."
- "**Addiction is used to connote a severe degree of drug dependence that is an extreme on a continuum of involvement with drug use.** The term conveys a quantitative rather than a qualitative sense of the degree to which drug use pervades the total life activity of the user and of the range of circumstances in which drug use controls the user's behavior. Anyone who is addicted would be considered drug dependent by the criteria described above. However, the term addiction cannot be used interchangeably with physical dependence as that term is used here. (bold by Takada)

9th edition, 1996 (by O'Brien)

- "Abuse and addiction have been defined and redefined by several organizations over

the past 25 years. The reason for these revisions and disagreements is that **abuse and addiction are behavioral syndromes that exist along a continuum from minimal use to abuse to addictive use.** While tolerance and physical dependence are biological phenomena that can be defined precisely in the laboratory and diagnosed accurately in the clinic, there is an arbitrary aspect to the definitions of the overall behavioral syndromes of abuse and addiction. The most influential system of diagnosis for mental disorders is that published by the American Psychiatric Association (DSM IV, 1994). The APA diagnostic system uses the term substance dependence instead of addiction for the overall behavioral syndrome. Although widely accepted, this terminology can lead to confusion between physical dependence and psychological dependence. **The term addiction, when used in this chapter, will refer to compulsive drug use, the entire substance dependence syndrome as defined in DSM IV.** This should not be confused with physical dependence alone, a common error among physicians. Addiction is not used as a pejorative term; in fact, the journal *Addiction* is one of the oldest scientific journals in this therapeutic area.” (bold by Takada)

- “The APA defines substance dependence (addiction) as a cluster of symptoms indicating that the individual continues use of the substance despite significant substance-related problems. Evidence of tolerance and withdrawal symptoms are included in the list of symptoms, but neither tolerance nor withdrawal is necessary or sufficient for a diagnosis of substance dependence. Substance abuse, a less severe diagnosis, involves a pattern of adverse consequences from repeated drug use that does not meet criteria for substance dependence.”

Appendix C. Various definitions seen in dictionaries***C-1. Definitions of addiction in dictionaries of various languages***

To summarize the change in non-scientific usage of the word *addiction* (and *addict*, when available) in various countries, definitions seen in the dictionary are listed below. For historic changes of definitions as seen in Webster's Dictionary and the origin of the word, see Appendix A.

English

Ad·dic·tion	Pronunciation:	&-'dik-sh&n,	a-	Function:	<i>noun</i>
Date:					1599
1	:	the quality or state of being addicted < <i>addiction</i> to reading>			
2	:	compulsive need for and use of a habit-forming substance (as heroin, nicotine, or alcohol) characterized by tolerance and by well-defined physiological symptoms upon withdrawal; <i>broadly</i> : persistent compulsive use of a substance known by the user to be harmful			

(*Merriam-Webster Collegiate Dictionary 10th Edition*;
<http://www.britannica.com/bcom/dictionary/>; June 22, 2000)

Chinese

Yin: 1) addiction; habitual craving: He's too fond of the cup. 2) strong interest (in a sport or pastime): have a passion for ball games; He's crazy about swordsman fiction.
(Chinese-English Dictionary, Foreign Language Teaching and Research Press, Beijing, 1995)

Yin: 1) originally refers to a habit which is not good, e.g. cigarette smoking, alcohol drinking. 2) also generally refers to habitual interest (in ball game, opera, etc.)
(Encyclopedia of Chinese Language, Shanghai Dictionary Press, 1999)

Yin: habitual craving, addiction (especially used for drugs).

(English-Chinese Medical Dictionary, Shanghai Science and Technology Press, 1984; reverse translation of the Chinese the definition of the entry "addiction" in English)

French

Dépendance/Toxicomanie: Terme générique recouvrant les notions de physicodépendance, de psychodépendance et de pharmacodépendance
Dictionnaire de médecine flammarien 1975

Generic term covering notions of physical dependence, psychological dependence and pharmacodependence.

German

Sucht/Suchtabhängigkeit: Mehr passives, zwanghaftes Angewiesensein auf die Befriedigung eines Triebes ungeachtet des Verlustes an Selbstwert-u.

(*Umweltbezug. Neben Nikotinabusus, Triebentartungen, chronischem Alkoholmissbrauch Roche Lexikon Medizin 1984*)

A rather passive, coercive dependence (in the sense of "to be left to one's own resources") on the satisfaction of a desire (in the sense of "urge", "drive", similar to sexual) ignoring the loss of relatedness to both oneself and to one's environment.

References made to: nicotine abuse, degeneration of desire (in the sense of "perversion"), chronic alcohol abuse.

Japanese

Shiheki: 1. One's special tendency to do one's certain favorite thing 2. (med.) sick condition when a person is always seeking stimuli such as alcohol and drugs, and has come to produce withdrawal symptoms.

(Sanseido, Encyclopedic Dictionary JIRIN21, Sanseido, 1993)

Tan-deki: Indulge in unhealthy amusements and disregard the other (e.g. be addicted to sensual pleasure).

Chu-doku: Induction of functional disturbance by taking harmful materials or inhaling toxic drugs etc. Usage: strong addictive narcotics; food poisoning
(Sanseido's New Japanese Dictionary, 1997)

Addiction: Shiheki (physical or psychological habitual dependence on a certain substances or conduct which is out of control)

(Stedman's Medical Dictionary 4th Ed., English-Japanese/Japanese-English, Tokyo, Medical Review, 1997)

C-2. Historic changes in definitions in Webster's dictionary of English languageWebster's 1828 Dictionary**ADDIC'TION, n.**

1. The act of devoting or giving up in practice; the state of being devoted.

His *addiction* was to courses vain.

2. Among the Romans, a making over goods to another by sale or legal sentence; also an assignment of debtors in service in their creditors.

Webster's 1913 Dictionary**Addiction**

Ad*dic"tion (#), n. [Cf. L. *addictio* an adjudging.] The state of being addicted; devotion; inclination. His *addiction* was to courses vain." Shakespeare

Addict

[imp. & p. p. Addicted; p. pr. & vb. n. Addicting.] [L. *addictus*, p. p. of *addicere* to adjudge, devote; ad + *dicere* to say.]

To apply habitually; to devote; to habituate; -- with to. They *addict* themselves to the civil law." *Evelyn*. He is **addicted** to his study. *Beau.* & *Fl.* That part of mankind that **addict** their minds to speculations. *Adventurer*. His genius **addicted** him to the study of antiquity. *Fuller*. A man gross . . . and **addicted** to low company. *Macaulay*.

Webster's Third New International Dictionary of the English Language (1961)

Addiction

1. Obs, INCLINATION, BENT

2a. The quality or state of being addicted *specif:* the compulsive uncontrolled use of habit-forming drugs beyond the period of medical need or under conditions harmful to society (the extent of *addiction* ranged from 2 months to 10 years)

2b. Enthusiastic devotion, strong inclination, or frequent indulgence (his *addiction* to comics) (his *addiction* to vivid metaphors)

3. [L *addiction-*, *addictio*, fr. *addictus* + -ion, -io -ion] : A formal award or assignment of a person or thing to another; *esp.*: an award made by a praetor or other magistrate (as of a debtor to a creditor)

Merriam-Webster Collegiate Dictionary 10th Edition

(<http://www.britannica.com/bcom/dictionary/> ; June 22, 2000)

Ad-dic-tion

Pronunciation:	&-'dik-sh&n,	a-
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Function:		<i>noun</i>
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Date:		1599
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1 : the quality or state of being addicted <*addiction* to reading>

2 : compulsive need for and use of a habit-forming substance (as heroin, nicotine, or alcohol) characterized by tolerance and by well-defined physiological symptoms upon withdrawal; *broadly* : persistent compulsive use of a substance known by the user to be harmful

C-3. The origin of the word addiction

(World Wide Words; an excerpt from <http://www.quinion.com/words/index.htm>):

"To start with, in the sixteenth century, *addict* was an adjective, not a noun. It came from the Latin *addictus*, the past participle of *addicere*. In this the root *dicere* meant 'to say', but it also had a sense of 'adjudge' or 'allot', so that the whole word meant 'assigned by decree'. (*Dicere* is the root also of our *dictate* and *dictionary*, so that the phrase "addicted to dictionaries" might be thought an unnecessary repetition.) The English word *addict* to start with had the sense of being obligated or formally bound to someone else. Pretty soon,

though, it took on a reflected meaning of being attached to something through one's own inclination, or of being devoted to some practice. Examples in the OED down to 1790 refer to gluttony, lust, and "superstitious ceremonies".

The book *Coined by Shakespeare* says Shakespeare was the first recorded writer to use *addiction*, as a relatively neutral word with a sense something like "strong inclination"; in *Henry V*, the Archbishop of Canterbury could marvel at the king's knowledge of theology, since before then "his addiction was to courses vain", meaning he used to like activities of no value or importance. By the 1640s, it was being used in a similarly straightforward way to indicate that one was given to some habit or pursuit; as late as 1858, Gladstone could write about "Their addiction to agricultural pursuits" and this sense remains in use just as much today.

The adjectival form of *addict* is long defunct, but the word was pulled out of retirement at the beginning of the twentieth century as a noun for someone whose inclinations towards or devotion to a drug has led to dependence upon it. A new word was needed because it was only at this period that the medical condition was being recognised and concern was beginning to grow. Only a few years after it had been reinvented it began to be used again in the old sense in which *addiction* has for so long been employed, of someone who is merely devoted to some activity, especially a pastime or sport: the OED has an example from the *Westminster Gazette* of 1925: "Even many working men are night club addicts". It is this looser, colloquial usage that concerns the researchers, because they feel it has become more common in the past decade or so. They claim that as a result people are becoming confused about the distinction between addiction and some harmless hobby or activity taken a little too seriously.

The lexicographical evidence is against them. There seems no very strong evidence that usage of *addict* or *addiction* in what must now be called its figurative sense has changed much in the past decade. And it's clear from the evidence that the word has had this figurative meaning for centuries, and that it long predates the modern meaning which they take as its canonical one. The concern about drug addiction this century has biased our understanding of the word, but the sense they worry about has been there all along."

C-4. Description in *Encyclopedia Britannica*

drug use (<http://www.britannica.com/bcom/eb/article/4/0,5716,118684+1.00.html>)

use of drugs for psychotropic rather than medical purposes. Among the most common psychotropic drugs are opiates (opium, morphine, heroin), hallucinogens (LSD, mescaline, psilocybin), barbiturates, cocaine, amphetamines, tranquilizers, and cannabis. Alcohol and tobacco are also sometimes classified as drugs. The term "drug abuse" is normally applied to excessive and addictive use of drugs. Because such drugs can have severe physiological and psychological, as well as social, effects, many governments regulate their use.

The nature of drug addiction and dependence

(<http://www.britannica.com/bcom/eb/article/4/0,5716,118684+2+110090,00.html>)

If opium were the only drug of abuse, and the only kind of abuse were one of habitual, compulsive use, discussion of addiction might be a simple matter. But opium is not the only drug of abuse, and there are probably as many kinds of abuse as there are drugs to abuse, or, indeed, as maybe there are persons who abuse. Various substances are used in so many different ways by so many different people for so many different purposes that no one view or one definition could possibly embrace all the medical, psychiatric, psychological, sociological, cultural, economic, religious, ethical, and legal considerations that have an important bearing on addiction. Prejudice and ignorance have led to the labelling of all use of nonsanctioned drugs as addiction and of all drugs, when misused, as narcotics. The continued practice of treating addiction as a single entity is dictated by custom and law, not by the facts of addiction.

The tradition of equating drug abuse with narcotic addiction originally had some basis in fact. Until recent times, questions of addiction centred on the misuse of opiates, the various concoctions prepared from powdered opium. Then various alkaloids of opium, such as morphine and heroin, were isolated and introduced into use. Being the more active principles of opium, their addictions were simply more severe. More recently, new drugs such as methadone and Demerol were synthesized but their effects were still sufficiently similar to those of opium and its derivatives to be included in the older concept of addiction. With the introduction of various barbiturates in the form of sedatives and sleeping pills, the homogeneity of addictions began to break down. Then came various tranquilizers, stimulants, new and old hallucinogens, and the various combinations of each. At this point, the unitary consideration of addiction became untenable. Legal attempts at control often forced the inclusion of some nonaddicting drugs into old, established categories--such as the practice of calling marijuana a narcotic. Problems also arose in attempting to broaden addiction to include habituation and, finally, drug dependence. Unitary conceptions cannot embrace the diverse and heterogeneous drugs currently in use.

Popular misconceptions

The bewilderment that the public manifests whenever a serious attempt is made to differentiate states of addiction or degrees of abuse probably stems from two all-too-common misconceptions concerning drug addiction. The first involves the stereotype that a drug user is a socially unacceptable criminal. The carry-over of this conception from olden times is easy to understand but not very easy to accept today. Ironically, the so-called dope fiend, if indeed one does exist, is likely to be a person who is not using an opiate. The depressant action of opium and its derivatives is simply not consistent with the stereotype. The second misconception involves the naïve belief that there is something magically druglike about a drug, which makes a drug a drug. Many substances are capable of acting on a biological system, and whether a particular substance comes to be considered a drug depends, in large measure, upon whether it is capable of eliciting a "druglike" effect that is valued by the user. There is nothing intrinsic

to the substances themselves that sets one active substance apart from other active substances; its attribute as a drug is imparted to it by use. Caffeine, nicotine, and alcohol are clearly drugs, and the habitual, excessive use of coffee, tobacco, or an alcoholic drink is clearly drug dependence if not addiction. The same could be extended to cover tea, chocolates, or powdered sugar, if society wished to use and consider them that way. The task of defining addiction, then, is the task of being able to distinguish between opium and powdered sugar while at the same time being able to embrace the fact that both can be subject to abuse. This requires a frame of reference that recognizes that almost any substance can be considered a drug, that almost any drug is capable of abuse, that one kind of abuse may differ appreciably from another kind of abuse, and that the effect valued by the user will differ from one individual to the next for a particular drug, or from one drug to the next drug for a particular individual. This kind of reference would still leave unanswered various questions of availability, public sanction, and other considerations that lead people to value and abuse one kind of effect rather than another at a particular moment in history, but it does at least acknowledge that drug addiction is not a unitary condition.

Appendix D. Evolution/history of PM position on the term addiction and how nicotine and/or smoking fit in.***Submission, 1994***

- "There is no consensus within the scientific community regarding the definition of the term "addiction." As a result, the characterization of a behavior as an "addiction" turns on one's choice of a definition rather than verifiable scientific findings."
- "Under a traditional and scientifically verifiable definition of "addiction," a substance is "addictive" if it causes (1) intoxication, (2) physical dependence (as manifested by a well-defined withdrawal syndrome), and (3) tolerance."
- According to this definition of "addiction," neither cigarette smoking nor the nicotine delivered in cigarettes is "addictive."
- "The effects of nicotine neither fully explain smoking nor justify characterizing smoking as a form of "drug-seeking" behavior."
- "Empirical evidence establishes that many other factors are equally or more important motivators of smoking behavior."

(Submission of Philip Morris USA and the American Tobacco Company to the Drug Abuse Advisory Committee in connection with its meeting on August 2, 1994, vol. 1.0 (July 29, 1994); citations from "Summary")

Before the United States Food and Drug Administration, 1996

- "Traditionally, the term "addiction" was reserved to describe the pharmacological phenomena of intoxication, tolerance, and a physical dependence that was manifested by withdrawal. Today, however, the concept of "addiction" is often indiscriminately applied to a seemingly endless array of products and activities."
 - Thus, although some researchers now argue that many behaviors can properly be labeled as "addictions,"¹⁷ others believe that only those involving the use of psychoactive substances should be considered as "addictions" or "dependencies."
 - The chapter titles of this document include the following:
 - "Cigarette smokers are not "addicted" under the traditional scientific definition of the term"
 - "Self-administration studies do not establish that nicotine is similar to addictive drugs"
 - "'Drug discrimination' studies and "liking"/"subjective effects" studies do not establish that nicotine is similar to addictive drugs"
- (Comments of Brown & Williamson Tobacco Corporation, Liggett Group Inc., Lorillard Tobacco Company, Philip Morris Incorporated, R.J.Reynolds Tobacco Company, Tobacco Institute Inc., Volume III, Docket Nos. 95N-0253, 95N-0253J,

April 19, 1996)

Position statement, 1997

- "We recognize that nicotine, as found in cigarette smoke, has mild pharmacological effects, and that, under some definitions, cigarette smoking is "addictive." The word "addiction" has been and is currently used differently by different people in different contexts, and the definition of the term has undergone significant changes over the past several decades. In 1964, for example, the Advisory Committee to the Surgeon General of the United States concluded that smoking, although "habit forming," did not fit within its definition of "addiction." However, in 1988, the Surgeon General redefined the term, and concluded that smoking is "addictive." We have not embraced those definitions of "addiction" which do not include historically accepted and objective criteria, such as intoxication and physical withdrawal, as important markers."
- "We acknowledge that our views are at odds with those of the public health community, but in the last analysis there is little point to a continuing public debate about the definition of a word used both colloquially and technically to describe many different kinds of behavior. We continue to believe that people can quit smoking if they resolve to do so, but we recognize that it can be difficult to quit. Accordingly, to ensure that there is a single, consistent public health message on the issue of addiction, we will refrain from debating the issue other than as necessary to defend ourselves and our opinions in the courts and other forums in which we are required to do so..."
(Industry submission to U.S. Senate Judiciary Committee, Philip Morris' Statement of Position, October 2, 1997)

PM website, 1999

"Cigarette smoking is addictive, as that term is most commonly used today."

(<http://www.philipmorris.com>)

Szymanczyk's testimony Engle June, 2000

"Q. Well, what's your definition of addiction?

A. Well, my definition of addiction is a repetitive behavior that some people find difficult to quit. Sometimes that's associated with a psychoactive drug, which is the case of nicotine in a cigarette, but people – some people are addicted to alcohol, but they quit drinking. They stop drinking alcohol.

And I don't – I don't think your definition of addiction, that you can't quit, makes any sense at all. I've never seen anybody who's concluded that that's what addiction means, that you can't quit."

"Q. Okay. That's how it's described.

And, of course, we're not talking about anything similar to heroin addiction or cocaine addiction; the common-day usage of addiction to you is like -- like coffee --

A. Well, I didn't say that.

Q. -- rather than like heroin?

A. I wouldn't say that. I wouldn't put it in the camp of heroin, but I've never used heroin, so it would be hard for me to determine that.

But I said it's a -- a repetitive behavior that some people find hard to quit, and it's associated with something that's psychoactive, and that's the case with nicotine."

Deposition of Parrish, Blue Cross and Blue Shield v. Philip Morris, June 14, 2000/08/04

"Q. The website uses the term, "Cigarette smoking is addictive as that term is most commonly used today." Do you know what is meant by the phrase, "as that term is most commonly used today"?

A. I believe it means that if someone continues to use a product or engage in an activity believing that it is harmful to you, and in the face of a desire to stop, that that activity or that substance is addictive. That's how I would explain it."

Appendix E. What do we know about smoking behavior?

Note: In parenthesis is the name(s) of participant(s) who will lead to complete/update each section.

1. Reinforcing effects of nicotine (Gullotta/Takada)**Animal studies**

- In an article entitled "The scientific case that nicotine is addictive", Stolerman (1995) described that:
 - "Solutions of pure nicotine can, in appropriate conditions, serve as a positive reinforcer in six different species (rats, rhesus monkeys, squirrel monkeys, baboons, dogs and humans....In some experiments, rates of responding maintained by the reinforcing effect of nicotine approximate to those maintained by cocaine under the same condition..." (Stolerman 1995, Psychopharmacol 117: 2-10).
 - "In other studies, nicotine has shown only rather weak efficacy as a positive reinforcer, and some reports have been negative...These findings have led some people to conclude that nicotine has little efficacy as a reinforcer and that there must be other explanations for the use of tobacco products. It is difficult to maintain that non-drug factors do not play any role in tobacco use, but the positive reinforcing effect of nicotine cannot be discounted as being of primary and fundamental significance." (*ibid.*).
 - "The available information suggests that nicotine is a weaker reinforcer than some classical drugs such as cocaine....Thus, nicotine is powerfully efficacious under only a relatively narrow range of conditions and self-administration is often slow to develop...The weakness of the effects of nicotine relative to those of classical drugs is puzzling and the reasons are not understood." (*ibid.*).
- In the continuous intravenous self-administration experiment in rhesus monkeys, it has been reported that:
 - "The daily intake pattern was quite stable with relatively frequent intake during the lights-on period, and very low intake during lights off. The daily dose levels were also stable in each monkey, but varied among monkeys in the range of 200-2000 µg/kg. No tendency of gradual increase or decrease was observed in them. During active intake of nicotine, no manifestation of drug effects was observable, and the gross behavior remained as usual." (Yanagita et al., 1983, Psychopharmacol Bull 19: 409-412).
 - "Progressive ratio test. The monkeys showed such high rates as 6400-12800 for the cocaine, and the rates paralleled unit dose. In contrast, no meaningful increase of the rate over saline was observable with the unit dose of nicotine 50 µg/kg. At 200 µg/kg, slightly higher rates, up to 1600, were obtained" (*ibid.*).
 - "The intensity of the intravenous drug-seeking behavior for nicotine observed in a progressive ratio experiment was found to be quite strong but weaker than that for

morphine or cocaine. Pretreatment with frequent intravenous doses of nicotine for 4 weeks did not enhance the intensity. This result demonstrates marked difference between physical dependence on opiates such as morphine or codeine and on nicotine." (Yanagita et al., 1991, In Adlkofer (ed), Effects of Nicotine on Biological Systems, pp. 433-442).

- Regarding the aversive effects of nicotine, it has been reported that "The response-produced i.v. injection of nicotine functioned effectively to suppress food-maintained responding by squirrel monkeys during the punishment component of a multiple schedule.", and that "In previous studies which demonstrated reinforcing effects of nicotine in squirrel monkeys (ref.), nicotine injections were substituted for saline injections while responding was occurring at very low rates, each injection of nicotine occurred only after a relatively long sequence of responses and there was a specified minimum period of time between successive injections. Whether nicotine functions as a punisher to suppress behavior or as a reinforcer to maintain behavior may be influenced by such difference in the schedule of injection." (Goldberg and Spealman, JPET 224: 334-340, 1983).
- The positively reinforcing and aversive effects have been observed at 10 ug/kg or more, with the highest response rate being observed at 30 ug/kg . Since both effects were not observed at 3 ug/kg, the threshold dose appear to be between 3 to 10 ug/kg (e.g. Goldberg et al., PBB 19: 1011-1020, 1983).

Human studies

- In an intravenous self-administration of nicotine at 0.75-3 mg/kg (1.5 mg injection was 18-22 ug/kg of body weights of the subjects), it has been reported that "Nicotine injections were taken in orderly patterns that were related in unit dose, whereas patterns of saline injections varied widely." (Henningfield et al., PBB 19: 887-890, 1983). In this report the number of self-administration during the 3-hr session in 5 subjects ranged from 8 to 29 for nicotine 1.5 mg and that of saline appears to have ranged from 4 to 37.
- Intravenous nicotine at 0.75-3 mg reportedly increased scores of morphine-benzedrine group (MBG) scale, a measure of euphoria, as well as LSD-scale, a measure of dysphoria, of the Addiction Research Center Inventory (ARCI) in "linear functions of dose" (Henningfield et al., JPET 234: 1-12, 1985).
- As in the animal studies, aversive effects of nicotine have also been observed in humans:
 - "Human volunteers were testedNicotine was found to maintain responding that produced its injection under certain conditions, and to maintain responding that avoided its injection under other conditions." (Henningfiled & Goldberg, 1983, PBB 19: 1021-1026)

- "Since nicotine can function either to maintain or suppress responding which produces its injection or to maintain responding that prevents its injection, it is not surprising that the precise effects of nicotine in the control of human smoking behavior have been difficult to determine. The nature of the control of smoking by nicotine is probably modified in response to changing environmental conditions." (Goldberg et al., PBB 19: 1011-1020, 1983)

2. Biochemical changes in the brain induced by nicotine (*Davies - to be completed*)

- In rats it has been reported that systemic nicotine increases extracellular DA level in midbrain, e.g. Nacc. Although it is hard to compare the precise of level of increase in microdialysis experiments, it appears that the level is much lower than that after e.g. cocaine.
- Domino states that raclopride did very little in the monkey brain (letter dated Apr 2000). "In conclusion, Domino remarked that very little is known about what goes on in the brains of tobacco smokers and more research on the role of NNRs in addiction is required." (Clementi et al., 2000, TiPS 21: 35-37; NNRs for neuronal nicotinic receptors)

3. Withdrawal signs after chronic nicotine treatment and smoking cessation (*Takada*)

Animal studies

- In rodents, Malin and others have reported several studies which describe withdrawal signs after cessation of continuous subcutaneous infusion of nicotine tartrate at 3-9 mg/rat/day. These signs include teeth-chattering/chews, writhes/gasps, ptosis, tremors/shakes, and yawns (e.g. Malin et al., PBB 43: 779-784, 1992). These authors also reported that similar signs have been observed after the administration of mecamylamine as well as naloxone during the chronic nicotine infusion (e.g. Malin et al., Psychopharmacol 115: 180-184, 1994). However, as for the nicotine withdrawal, as the authors described, "Surprisingly few animal models have been described, and these rely either on changes in conditioned behavioral responses (ref) or changes in body weight and food consumption (ref)." This observation as well as the reported withdrawal signs in rodents appear to indicate that the physical dependence potential of nicotine is weak.
- Indeed, in rhesus monkeys, it has been reported that chronic nicotine treatment (hourly injection at 0.25 mg/kg, i.v. for 4 weeks) did not produce any appreciable changes in grossly observable behavior nor the increase in reinforcing efficacy of nicotine, as cited above (Yanagita et al., 1991, In Adlikofer (ed), Effects of Nicotine on Biological

Systems, pp. 433-442). The effects of mecamylamine in these monkeys were not distinguishable from saline control (Takada, unpublished observation).

Human studies

- No data on chronic treatment of pure nicotine is available.
- Diagnostic criteria for nicotine withdrawal in DSM-IV are: "Four (or more) of the following signs" followed within 24 hrs of abrupt cessation of nicotine use (smoking); 1) dysphoric or depressed mood, 2) insomnia, 3) irritability, frustration, or anger, 4) anxiety, 5) difficulty concentrating, 6) restlessness, 7) decreased heart rate, and 8) increased appetite or weight gain.
- Hughes and Hatsukami reports that "we believe the valid signs and symptoms of tobacco withdrawal are craving for tobacco, irritability, anxiety, difficulty concentrating, restlessness, bradycardia, and increased eating". However, these authors also stated that "The clinical significance of tobacco withdrawal is also unknown." (Hughes and Hatsukami, cited above).

4. Pharmacological intervention of smoking behavior in humans (Ritter/Takada)

- Nicotine given i.v. or via nasal spray and mecamylamine given s.c. have been reported to alter smoking behavior in humans.
- Pharmacological intervention including the nicotine replacement therapy and the treatment of other pharmacotherapeutic agents e.g. buspirone and bupropion *in conjunction with* behavioral modification to help smoking cessation resulted in the success rate of 30-40% at most, which again suggest that nicotine may not be the sole determinant of smoke exposure.

5. Sensory aspects (Gullotta)

- Both cigarette smoking and peripheral administration of nicotine stimulates the sensory branches of five of the twelve cranial nerves:
 - In the mouth, smoking and nicotine stimulate the chorda tympani, glossopharyngeal and trigeminal nerves.
 - In the throat, smoking and nicotine stimulates the glossopharyngeal and vagus nerves.
 - In the nose, smoking and nicotine stimulates the olfactory and trigeminal nerves.
- Given the fact that smoking and nicotine stimulate so many nerves it should not be surprising that both smoking and nicotine have pronounced flavor properties.
- With respect to nicotine, when applied to the tongue at concentrations found in smoke,

it produces a bitter sensation.

When nicotine vapors are applied to the nose it produces a concentration-dependent effect:

- at low concentrations it produces an odor of pyridine;
- at higher concentrations, it produces an odor plus burning;
- at still higher concentrations, it produces odor plus burning plus stinging.

When nicotine, as delivered in cigarette smoke, is delivered to the back of the throat, it produces the sensation of impact, via stimulation of the glossopharyngeal and vagus nerves.

- In addition to nicotine and smoke's well-known pharmacological properties, it should be obvious from the discussion above that nicotine and smoke have diverse sensory properties. The relative contributions of pharmacology and sensory physiology to the enjoyment of smoking is currently unknown. An experiment would need to be conducted where a centrally inactive sensory substitute for nicotine was used. Unfortunately, at present such a substitute does not exist.

Appendix F. Disease criteria (ICD-10 and DSM-IV)

Table. Criteria for "Dependence syndrome" in ICD-10 and "Substance dependence" in DSM-IV are shown.

ICD-10	DSM-IV
Dependence syndrome: characterized as a cluster of effects after repeated use of a substance resulting in three or more of the following symptoms:	Substance Dependence: A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period
1. a strong desire or sense of compulsion to take the substance	(4) there is a persistent desire or unsuccessful efforts to cut down or control substance use
2. an impaired capacity to control substance-taking behavior in terms of its onset, termination, or levels of use; substance use with the intention of relieving withdrawal symptoms and with awareness that this strategy is effective	(5) a great deal of time is spent in activities necessary to obtain the substance (e.g., visiting multiple doctors or driving long distances), use the substance(e.g., chain-smoking), or recover from its effects
3. a physiological withdrawal state	(1) withdrawal, as manifested by either of the following: (a) the characteristic withdrawal syndrome for the substance (refer to Criteria A and B of the criteria sets for Withdrawal form the specific substances) (b) the same (or closely related) substance is taken to relieve or avoid withdrawal symptoms
4. evidence of tolerance such that the increased doses of the substance are required in order to achieve effects originally produced by lower doses	(2) tolerance, as defined by either of the following: (a) a need for markedly increased amounts of the substance to achieve intoxication or desired effect (b) markedly diminished effect with continued use of the same amount of the substance (3) the substance is often taken in larger amounts or over a longer period than was intended
5. Progressive neglect of alternative pleasures or interests in favor of the substance	(6) important social, occupational, or recreational activities are given up or reduced because of substance use
6. Persisting with substance use despite clear evidence of overtly harmful consequences	(7) the substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance (e.g., current cocaine use despite recognition of cocaine-induced depression, or continued drinking despite recognition that an ulcer was made worse by alcohol consumption)

"Nicotine Dependence" is characterized as follows in the DSM-IV:

- Nicotine Dependence

"...Some of the generic Dependence criteria do not appear to apply to nicotine, whereas others require further explanation... Many individuals who use nicotine take nicotine to relieve or to avoid withdrawal symptoms when they wake up in the morning or after being in a situation where use is restricted.... Individuals who smoke and other individuals who use nicotine are likely to find that they use up their supply of cigarettes or other nicotine-containing products faster than originally intended.."

- Nicotine-Induced Disorder

292.0 Nicotine Withdrawal

"These symptoms are in large part due to nicotine deprivation... The more rapid onset of nicotine effects with cigarette smoking leads to a more intensive habit pattern that is more difficult to give up... Mild symptoms of withdrawal may occur after switching to low-tar/nicotine cigarettes..."

- Among various compounds, characteristics of nicotine in relation to "substance dependence" is summarized in the following table in DSM-IV (modified by Takada – see the note in the Table).

DSM-IV, APA 1994

Table 1. Diagnoses associated with class of substances¹⁾

	#Category	Depen- dence	Abuse	Intoxi- cation	With- drawal	Intoxic- ation Delirium	With- drawal Delirium	Dementia	Amnestic Disorder	Psychotic Disorders	Mood Disorder	Anxiety Disorders	Sexual Dysfunc- tions	Sleep Disorders
Polysubstance	1	X												
Nicotine	2	X			X									
Caffeine	3			X								I		I
Cannabis	6	X	X	X		I				I				
Hallucinogens	7	X	X	X		I				I*	I			
Phencyclidine	7	X	X	X		I				I	I			
Inhalants	8	X	X	X		I		P		I	I			
Opioids	9	X	X	X		I				I	I		I	IW
Amphetamines	10	X	X	X	X	I				I	IW	I	I	IW
Cocaine	10	X	X	X	X	I				I	IW	IW	I	IW
Alcohol	13	X	X	X	X	I	W	P	P	IW	IW	IW	I	IW
Sedatives, hypnotics, or anxiolytics	13	X	X	X	X	I	W	P	P	IW	IW	W	I	IW
Other	13	X	X	X	X	I	W	P	P	IW	IW	IW	I	IW

* Also Hallucinogen Persisting Perception Disorder (Flashbacks)

Note: X, I, W, IW, or P indicates that the category is recognized in DSM-IV. In addition, / indicates that the specifier With Onset During Intoxication may be noted for the category(except for Intoxication Delirium); W indicates that the specifier With Onset During Withdrawal may be noted for the category (except for Withdrawal Delirium); and IW indicates that either With Onset During Intoxication or With Onset During Withdrawal may be noted for the category. P indicates that the disorder is Persisting.

1) The order of listing was modified by Takada

#Category-Number of categories recognized in DSM-IV shown in the table; added by Takada to the original list.